REMARKS

Applicants respectfully request reconsideration of the instant application in view of the following remarks. Claim 1 has been amended to correct minor typographical errors. Accordingly, this response does not introduce any new matter into the application.

The instant invention is directed, inter alia, to a method for determining receptivity of the endometrium for implantation, the method comprising the steps of isolating RNA from a blood sample or tissue sample and quantitatively measuring in said blood sample or said tissue sample the expression or over expression of mRNA of at least one of β7-hCG, β6-hCG, and β6e-hCG, determining the receptivity as follows: if no β7-hCG, β6-hCG, and β6e-hCG is detected, then the endometrium is not receptive, and if at least one of β7-hCG, β6-hCG, and β6e-hCG is detected, then the endometrium is receptive for implantation.

The sole outstanding reason for rejection in the instant application is a rejection based on alleged non-compliance with 35 U.S.C. § 112, 1st paragraph (enablement).

The test of enablement is whether the disclosure of the application enables a person of ordinary skill in the art to make and use that which is defined by the claims, coupled with information known in the art, without undue experimentation. MPEP § 2164.01, *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988).

Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). Therefore, the Examiner has to consider not only the instant disclosure but also the knowledge accumulated in the prior art in the areas of mRNA detection, endometrial receptivity and hCG effects.

1. The Examiner has not provided reasonable basis for doubts regarding the truth of the instant disclosure.

The burden of establishing non-enablement is on the Examiner. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocci,* 439

F.2d 220, 223 (C.C.P.A. 1971). If such reason exists, the Examiner has to explain why she doubts the truth or accuracy of any statement is the supporting disclosure. MPEP § 2164.04.

In the instant case, the Examiner bases her argument of non-enablement on the doubts regarding the correctness of the disclosure, and to support her argument, she brings five references, applicability of which will be discussed below. The first reference is Lindhard et al *Fertil. Steril.* 78(2): 221-223 (2002). Applicants respectfully note that the Examiner assumes that this article provides an exhaustive list of endometrial factors assumed to be of importance in implantation. However, Applicants respectfully challenge this assumption and ask the Examiner to provide the justification for her assumption. At the same time, Applicants respectfully note that Lindhard omitted many other markers of endometrial receptivity to implantation. For example, Lindhard omitted at least one family of factors, namely HOX genes which have been known to be "important for human endometrial development and receptivity." See Taylor, *Human Reproduction Update*, 2000, 6(1): 75-79. Thus, it is impossible to conclude that hCG is not important for endometrium receptivity simply because it was not mentioned in Lindhard.

Acosta, *Fertil. Steril.* 73(4): 788-798 (2000) specifically states that "a fair number of biomarkers [in human endometrium that seem to participate in the implantation process] have been described in literature" and disclosed a few which were found to have clinical significance at the date of publication, which is three years earlier than the filing date of the instant application. See Acosta at 789, Right Col. Acosta discloses certain cytokines, mucin (MUC-1), MAG, and receptors for E_2 and P_4. Again, it is impossible to draw a logically valid conclusion from Acosta for at least two reasons: first, Acosta himself states that the markers described in the article were not exclusive markers, and second, significant progress have been made in three years since Acosta publication to the filing of the instant application.

Next, the Examiner refers to Licht et al, *Fertil. Steril.*, 79 Suppl. 1: 718-723 (2002) and Fazleabas et al, *Proc. Natl Acad. Sci.*, 96: 2543-2548 (1999). She admits that it is clear that hCG acts on endometrium and that exogenous hCG levels influence endometrium receptivity and implantation. However, the Examiner argues that the expression of hCG in the endometrium itself can be correlated with the receptivity of endometrium for implantation. Applicants respectfully question that conclusion. If exogenous hCG is important for the receptivity of endometrium to implantation, as admitted by the Examiner on p. 11 of the Office Action, why wouldn't endogenous hCG also be important for the same purpose?

Finally, the Examiner relies on Coutifaris et al., *Fertil Steril.* 82(5): 1264-1272 (2004) to argue that histological dating of timed endometrial biopsy is not related to fertility status. Applicants would like to respectfully point out at least two flaws in the Examiner's reasoning and in Coutifaris's data analysis.

First, it is unclear how this conclusion relates to a fact that hCG is not a marker for endometrial receptivity.

Second, Coutifaris used criteria of Noyes to date the biopsies. Coutifaris, at 1266, Right Col. Thus, in essence, Coutifaris concludes that Noyes's criteria do not provide clinically useful information. Noyes was published fifty years prior to the publication of Coutifaris (see reference 22 in Coutifaris) and his criteria have been criticized as far back as 2000. See Acosta, at 788, Left Col. In view of that fact, the statement on page 1271 cited in the Office Action at page 11 is correct only to the extent that Coutifaris states that additional research (i.e., research for the markers established in addition to Noyes over fifty years ago) are encouraged in this field. However, Applicants respectfully maintain that Noyes is an outdated reference and tremendous progress has been made since 1950. For example, Applicants refer the Examiner to Licht and Fazleabas, discussed above, for the information that exogenous hCG influences endometrium receptivity for implantation.

As discussed in MPEP § 2164.04,

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Emphasis added. Thus, the explanation should be based on some reasons, and in such science-intense field as biology, the Examiner's reasons should be scientifically based. In this case, the Examiner provides five articles, which have been analyzed before and can be summarized as follows: two articles (Acosta and Lindhard) do not recite all receptivity markers, two (Licht and Fazleabas) establish that exogenous hCG influences endometrium receptivity for implantation, thus supporting the conclusion that endogenous hCG would have the same function, and one (Coutifaris) is inconclusive and relies on outdated and criticized criteria.

Thus, the Examiner's reasons do not withstand proper logical, legal, and scientific analyses. Accordingly, for these reasons, Applicants respectfully submit that the Examiner has

not established proper reasonable basis to doubt the truth of the Applicants' disclosure and therefore, the instant rejection ground should be withdrawn.

2. Analysis of Wands factors.

As discussed above, the test of enablement is whether the disclosure of the application enables a person of ordinary skill in the art to make and use that which is defined by the claims, coupled with information known in the art, without undue experimentation. Federal Circuit established several factors which may be considered in order to make the conclusion of enablement. These factors were specified in *In re Wands*, and include the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The analysis of Wands factors should consider the whole record and the conclusion should be based on the evidence as a whole.

Since the Examiner has not established the proper basis to question the truth of the Applicants' assertion, and therefore, has not fulfilled her burden, for the completeness of the response, Applicants provide analysis of *Wands* factors below.

The scope of the claims

In this case, the scope of the claims is very precise: the claims are drawn to measuring β7-hCG, β6-hCG, β6e-hCG in blood or tissue sample of a subject, wherein the presence of at least one of those species indicates that the subject's endometrium is receptive for implantation, and the absence of all three species indicates that the subject's endometrium is not receptive for implantation. Thus, this precise scope of the claims leads to a conclusion that this *Wands* factor favors the finding of enablement.

The nature of the invention

In this case, the invention is in the field of diagnostic techniques related to reproductive biology. The diagnostic techniques in general (e.g, variations of quantitative PCR) and detection of hCG in general (e.g., pregnancy tests) are well known in the art. Accordingly, this *Wands* supports the finding of enablement.

The state of the prior art and the predictability of the art

The Examiner notes that she has carefully looked through the specification and did not see any data that would allow one of ordinary skill to determine the correlation between the detection of mRNA species recited in the claims and the receptivity of the endometrium. Office Action at 8. The Examiner also asserted that she would like to see the data where expression of these mRNA species correlates with the receptivity of endometrium. Applicants respectfully note that this is an arbitrary requirement imposed by the Examiner contrary to MPEP (see, e.g., MPEP § 2164.04). As discussed above, the burden of establishing non-enablement is on the Examiner. In addition, MPEP § 2164.05 states, in relevant part, that

> [o]nce the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art.

Three procedural issues are resolved in this quote. First, Applicants do not have to provide any arguments before the Examiner has established a reasonable basis for doubting the instant disclosure. In this case, the Examiner has not done it, as illustrated above. Second, Applicant is not required to show any new data (i.e., persuasive arguments are sufficient). In this case, Applicants provided argumentation challenging the Examiner's "reasonable basis" as discussed above, and also provided affirmative evidence from the references on the record, which evidence favors the finding of enablement. Third, the evidence provided by the Applicant does not need to be conclusive, and therefore, the Examiner's imposition for clinical data is improper.

The Examiner argues that since the invention is in the field of biology and since biology in general is an unpredictable art, the art is unpredictable in the field of diagnostic techniques related to reproductive biology. Applicants respectfully note that this general statement is not a substitute for the analysis of the situation in the instant case. See, e.g., *Ex parte Forstova*, Appeal No. 1998-0667, where the Board overturned a rejection based on non-enablement, which rejection was based on the Examiner's assertion that generally gene therapy is unpredictable.

In this case, the evidence provided by the Examiner has been summarized above. This evidence consists of five articles, two of which (Acosta and Lindhard) are inconclusive (at least because the list of the endometrial markers recited therein is not exhaustive), one (Coutifaris) relies on an outdated technique which has been criticized recently, and two of these articles (Licht and Fazleabas) support the notion that exogenous hCG is important for endometrium receptivity, as admitted on page 11 of the Office Action). Thus, if anything, the prior art is predictable with respect to the effect of hCG on the endometrium. In view of these findings, applicants respectfully re-iterate their request for the Examiner to provide reasoning supporting a conclusion that the effect of endogenously expressed recited hCG species is unpredictable even though one can predict the effect of the exogenous hCG.

At the same time, Applicants provided multiple references (on record) which demonstrate reliability (and predictability) of diagnostic techniques. See, e.g., Giovangrandi et al., *Cancer Letters*, 168: 93-100 (2003), discussing real-time quantitative RT-PCR of hCG in breast cancers, and Hotakainen et al., *Brit. J. Cancer* 86: 185-189 (2002).

Even though Applicants do not need to comply with the requirement for the additional data, which requirement is contrary to MPEP, and solely in the interest of expediting the prosecution of the instant application, Applicants further disclose additional data in support of the instant claims.

In 2003, Applicants obtained over 200 tissue samples of biopsies of the Endometrium of healthy women. These samples were taken in the fertility center of the "Universitätsfrauenklinik" at Leipzig, Germany. Samples of the different patient groups in different phases of a healthy, menstrual cycle were as follows: normal, proliferative (n=60) and normal, secretory transformation phase (n=145). The latter was subclassified in groups of normal, very early and early secretory (n=42); middle secretional (n=35); late secretory (n=30) and late secretory predezidual phase (n=38).

In a representative subset of samples from 81 patients (22 patients in proliferative phase, 28 patients in early secretory phase, 26 in midsecretory phase, and 15 in late secretory phase), Applicants discovered that while βhCG mRNA was essentially absent during the proliferative phase, its level increased by over ten fold at the Early secretory phase, increased further by about 2.5-3 fold at the Midsecretory phase, and stayed about the same at the Late secretory phase.

Thus, in the time window when implantation occurs in the course of a normal pregnancy, βhCG is at its highest concentration.

In another set of experiments, the levels of the βhCG subunit were determined as an endometrial βhCG score (0 to 4, wherein "0" represents the lowest βhCG concentration) by immunohistological staining. This staining was correlated with the development and differentiation of endometrium during the menstrual cycle. Specifically, Applicants discovered that the endometrial βhCG was absent during proliferative phase, and that its staining intensified and its secretion increased during the early secretory and mid secretory phases. Applicants also discovered strong glandular hCG secretion in functionalis and predecidual luminal ands apical endometrium areas of the late secretory phase. The increased βhCG staining correlated with cycle-adequate glandular shape transformation, epithelial nuclear differentiation, increasing leukocyte number (as verified by CD-45 staining), vascular differentiation in endometrial stroma and epithelium (as verified by CD-34 staining), and endometrial NK cell infiltration (as verified by CD-56 staining).

This evidence leads to a reasonable conclusion that endometrial βhCG may be used as a marker of endometrial receptivity for implantation.

In sum, the art on the record establishes reliability of diagnostic methods contemplated in the instant claims, establishes importance of exogenous hCG is important for endometrium receptivity, and lacks evidence that the recited β-hCG species behave differently from exogenous hCG. Additional data provided by Applicants establish that endometrial βhCG is expressed at a time when endometrium is receptive for implantation, and establish correlation of βhCG with other markers of receptive endometrium. Accordingly, this factor favors the finding of enablement.

Ordinary skill in the art.

It has been agreed that the level of skill in the relevant art is high. See Office Action at 13. Accordingly, extensive guidance is not needed for enablement of the claims. Therefore, this *Wands* factor favors the finding of enablement.

Guidance provided in specification

As discussed above, ordinary skill is high in the art of diagnostic related to implantation and the Examiner was unable to provide any evidence establishing that the relevant art is

unpredictable. Accordingly, extensive guidance is not needed for practicing the invention. See MPEP § 2164.03 ("The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.")

The specification discloses tissues or liquids suitable for the methods of the instant invention, teaches how to obtain samples of those tissues, provides ample guidance on mRNA extractions from the samples, discloses sequences for the recited hCG species and provides primers suitable for PCR amplification. The specification also states that "[t]he invention is based on the scientific finding that the level of expression of the genes of the type I-β-hCG (β7, β6, eβ6) in the normal secretory epithelium of the uterus lining (endometrium) or in the mononuclear cells of the peripheral blood represents a reliable indicator for a possible successful implantation." See the specification as published, US 20060292657, paragraph 0072. These teachings, taken together with the techniques of prior art and the knowledge that hCG is important for implantation, lead to a conclusion that this *Wands* factor also favor the finding of enablement.

Presence of Working Examples

The presence or absence of working examples is not dispositive of the issue of enablement. In fact, there is no legal requirement for reduction of invention to practice. See, e. g, MPEP § 2164.02 ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.") Accordingly, it is improper for the Examiner to reject the claims of the instant application simply because prior art does not disclose that type I-β-hCG is a marker of endometrial receptivity to implantation.

Applicants further submit that the standard for a proper experimental design of the examples in an application is lower than the standard applied by most, if not all, scientific peer-reviewed journals. For example, U.S.P.T.O. routinely allows and considers prophetic examples (wherein NO EXPERIMENTS AT ALL had been performed and the results and conclusions are based on the inventor's opinion and the knowledge of the prior art), while no respectable scientific journal would allow such thing.

Quantity of Experimentation

The Examiner asserts that "[b]efore the claimed method can be used by one of ordinary skill, appropriately designed controlled clinical trials would have to be concluded so that one of ordinary skill knows that mere detection of at least one …[of the recited molecules] is an indicator of receptivity of endometrium for implantation." Thus, the Examiner's position on this Wands factor is clear: the Examiner wants nothing short of clinical trials. This imposition is contrary to MPEP. First, MPEP § 2164 unequivocally states that "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." Internal quotation omitted. Clearly, there is no such limitation in the instant claims.

Second, the Examiner essentially wants FDA-related data for the support of the instant claims. This is contrary to MPEP § 2164.05 ("However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled.")

Applicants further submit that while the quantity of experimentation may be significant, this factor by itself is not sufficient to conclude that the claims are not enabled. See, e.g., MPEP 2164.06 ("[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "). In the instant case, the specification provides ample guidance for selecting the tissue, collecting the samples, extracting mRNA and quantifying the extracted mRNA. Considering that the skill in the relevant art is high, the guidance in the specification reduces the required experimentation to mere routine endeavor. Therefore, this *Wands* factor also favors the finding of enablement.

In sum, Applicants respectfully submit that the balanced analysis of the *Wands* factors leads to a conclusion that the claims of the application are enabled and respectfully request the Examiner to withdraw the instant rejection ground.

Applicants also respectfully submit that the Examiner's narrow interpretation of the enablement requirement is contrary to the spirit of 35 U.S.C. § 112, first paragraph, as evidenced by MPEP § 2164.08 (*Internal quotations omitted*):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials

> in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Accordingly, for at least these reasons, the claims of the instant application are enabled, and Applicants respectfully request the Examiner to withdraw the instant ground for rejection.

CONCLUSION

In view of these amendments and remarks, Applicants believe that the claims of this application are in condition for allowance and an early notice to this effect is earnestly solicited. If the Examiner does not believe that such action can be taken at this time or if the Examiner feels that a telephone interview is necessary or desirable, Applicants welcome the Examiner to call the undersigned at 609-844-3021.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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